Multiple Sclerosis – Disease of Mystery
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Introduction
The causes of multiple sclerosis (MS) have remained a mystery despite very extensive and intense research over a period of many years. There are, however, some very intriguing hints that suggest the possible nature of this disease. Basically, MS may arise from the chance similarity between antigenic groups found on certain viruses and antigens found on myelin, the insulating sheath covering nerves. Also involved is genetic predisposition to the disease in addition to unknown factors related to geographic locations.

Causative Factors in MS
In the Faroe Islands off the coast of Denmark, MS was completely unknown until a time period of approximately 20 years (1943-1961) following the Second World War. During the war the islands were occupied by British troops. The presence of the British brought about an epidemic of canine distemper (of virus origin). Similar reports of troop occupation accompanied by canine distemper and MS were noted in both Iceland and the Orkney/Shetland Islands. These observations do not indicate that the cause of MS is canine distemper but that some MS-causing infectious agent may be associated with both canine distemper and MS.1

The distribution of MS is related to latitude, increasing as one moves farther from the equator.2 In the US the geographical significance of the incidence of MS also applies to east and west.3

Investigations of populations moving from a high risk area (for example, the United Kingdom) to a low risk area (South Africa) had an MS occurrence similar to that of the UK population. In addition, the descendants of the UK immigrants had a much lower incidence of MS.

Similar surveys of children (aged 0-14) moved from the UK to South Africa showed that the risk of contracting MS in later life was much lower than that of the migrant adults. If migration occurred prior to adolescence, the child assumed the risk of the new geographical location.4

Several myelin-specific antigens, both protein and lipid, have been implicated in MS etiology. One of those most investigated is known as myelin basic protein (MBP). The term “basic” refers to the over-all electrical charge of the molecule (positive, or cationic). A small percentage of antibodies (4%) made against viral proteins also bind to certain parts of MBP. This is explained by a similarity between the amino acid sequence of viral proteins and those of certain sections of MBP.5,6 As further confirmation of this concept, immunization of an animal with MBP leads directly to the clinical and pathological condition of experimental allergic encephalomyelitis (EAE), an in vivo model of MS.1

The Nature of Myelin
Myelin is a lipid-protein membrane construct acting primarily as an electrical insulator for nerves. Myelin controls and increases the speed of signal transmission along the axon from the nerve cell body to the synaptic junction. This highly ordered spiral array of membrane and aqueous compartments can achieve an appreciable thickness of 5-20 multilayers.1

One of the major units of myelin mentioned briefly above is myelin basic protein (MBP) and has been very extensively studied. The amino acid sequence of human MBP has been determined and consists of 170 residues, some of which are capable of undergoing further modification such as phosphorylation and methylation (posttranslational modifications).

Myelin Formation
Myelin is a product of a specific type of cell lying among other neurological cells in white matter. The oligodendroglial cells direct processes of their plasma membranes to distant target axons.14 These fragile extensions establish a connection with an axon and proceed to envelop the axonal cylinder with a continuous wrapping of membrane. The cytoplasm, bounded by two lipid membranes, flows around the cylindrical axon. When the double-membrane cytoplasmic sheet flows completely around the axon, it contacts itself and, as it continues to flow, moves under the first layer. This spiraling process continues until 5-20 layers are added. Thus, the nerve cell (axon) is wrapped with the first material lying in contact with the axon while the last material is external. As wrapping continues, the first material wrapped (the innermost layers) are compacted and made much thinner than when first formed. More will be said about the compaction of myelin in the discussion of myelin basic protein.

A single oligodendroglial cell may produce many extensions of its membrane and provide myelin wrappings for more than one axonal cell. It is not known with certainty whether or not there remains a thread or connecting link between the oligodendroglial cell and the cell it is wrapping with myelin. These aspects of myelin formation may explain the inability of the oligodendrocyte to reinitiate myelination following membrane breakdown due to an enormous metabolic energy requirement. If a single oligodendrocyte dies, many axons are influenced by an inability to remyelinate these cells.42

Electrical Charge of MBP
MBP is a water soluble protein with a molecular weight of 18,500,8 accounts for approximately 25-30% of the total myelin protein and is the second most abundant species after the proteolipid proteins. It is contained exclusively within the cytoplasmic spaces of myelin.8 The high lysine and arginine content (both basic amino acids) gives the protein a net charge of +20 at physiologic pH.

Oxidation of MBP
One important aspect of the amino acid content of MBP is the presence of two methionine (Met) residues. These amino acids contain the C-S-C linkage which may be oxidized to the sulfone or sulfoxide by hydroxyl radical or other oxidizing agents. The result of Met oxidation is charge reduction.10 It is believed that the high negative charge of MBP is related to its activity in myelin, to be discussed more fully below.

Oxidative Stress in MS
Monocytes from MS patients produce significantly more hydrogen peroxide, superoxide10 and chemiluminescence (indicative of singlet oxygen) than normal individuals.11 Complementary to this finding is the increase in the enzyme that destroys superoxide (SOD) and a decrease in the enzyme that destroys hydrogen peroxide (glutathione peroxidase).12 The increase in SOD activity is the result of increased superoxide while the lowered activity of glutathione peroxidase leads to higher...
levels of hydrogen peroxide. These findings reveal that MS patients are under greater oxidative stress, increasing the occurrence of altered (oxidized) MBP.

**The Use of Antioxidants in Therapy**

These observations have two implications: (1) The increased presence of oxidizing agents in the blood of MS patients may have been a causative factor in the development of the disease through the chemical modification of at least one critical protein component of myelin (MBP), leading to autoimmune disease and (2) higher levels of oxidizing agents in the blood justify the use of antioxidants in a therapeutic program designed for MS.

**Methylation of MBP**

Analysis of MBP shows that it contains a methylated arginine (Arg) residue which may be important in the formation of normal myelin. In culturing those cells that generate myelin, inhibition of the enzyme responsible for methylation results in a significantly less compact myelin. It has also been noted that the degree of methylation correlates with an increased interaction of MBP with lipid vesicles.

**Structure of MBP**

MBP has very little self-related structure (conformation) in water. However, several sources of information have indicated that MBP-lipid interactions play a critical role in the formation of myelin. It appears that MBP is responsible for initiating the compaction process within the myelin cytoplasm as well as maintaining the closely apposed multilayers in the mature structure. The attraction between MBP and lipid is largely electrostatic. This emphasizes the significance of charge in the oxidation of MBP by abnormal oxidizing agents as mentioned above. The oxidation of MBP by hydroxyl radical and the resultant loss of charge leads to the dissociation of MBP and the loss of myelin integrity, allowing its further degradation and the onset of MS. The administration of antioxidants allows the formation of normal MBP and the regeneration of myelin.

MBP isolated from brain tissue of MS patients is often less cationic (positively charged) and relatively less efficient than normal protein in its ability to bind lipids.

Inoculation of guinea pigs with MBP results in experimental allergic encephalomyelitis (EAE) which has clinical implications indistinguishable from those of MS. As with MS, recovery from EAE is related to the ability of the host to produce effective suppressor T-cells to down-regulate the cytotoxic side of the immune reaction.

**Proteolipid Protein**

The proteolipid protein (PLP), also called lipophilin because of its ability to bind lipids, is a membrane protein with an approximate molecular weight of 30,000 and is the single most abundant protein of myelin. As with MBP, the amino acid sequence of PLP has also been determined.

It has been shown that MBP binds PLP in a reversible manner and that the binding was much greater for MBP than for other basic proteins. As with MBP, PLP has a functional role in relation to myelin compaction.

The amino acid sequence of PLP has been found to be similar to the sequences of a number of viral proteins including those of Epstein-Barr, influenza A, HIV and adenovirus polypeptides. Infection with any of these viruses or others having similar sequences leads to the production of antibodies which will also bind to similar sequences present in myelin proteins. As has been demonstrated in experimental MS (EAE), the presence of antibodies to myelin results in the symptoms of MS.

**Endotoxin May Be Instrumental in MS Etiology**

The oxidation of MBP and the effect on the structure of myelin is not the only significance of oxidative processes in MS. Experiments with animals have shown that myelin is damaged by either reactive oxygen toxic species (ROTS) or by the result of ROTS activity, namely, lipid peroxides. Other experiments have indicated that endotoxin, the lipopolysaccharide shed from the surface of certain bacteria, when administered to experimental animals, generates lipid peroxides. The toxic effect of endotoxin is believed to result from the production of oxygen free radicals (superoxide or hydroxyl radical generated by leukocytes stimulated by endotoxin).

If there is an association between intestinal infection by bacteria and damage to myelin by ROTS generated by certain white cells stimulated by bacterial endotoxin, there should be a correlation between diseases associated with endotoxemia and MS. Indeed, such a correlation has been described in relation to ulcerative colitis and MS.

It should also be realized that absorption of endotoxin does occur from the intestine. A number of abnormalities (dysbiosis) of the small bowel have been noted in MS patients as well as malabsorption problems.

**Dental Disease and MS**

An association between MS and dental disease has been published in the medical literature. Endotoxin has been associated, with dental plaque and gingival crevicular fluid as well as with necrotic pulps. It has been shown that endotoxin is absorbed across gingival tissue as well as by the intestine.

The association of endotoxin activity with dental disease is confirmed by a
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> study which associates serum copper levels with the severity of periodontal lesions in 80 dental patients. Endotoxin is known to also cause an increase in serum copper concentration.

Mycoplasma and MS

Mycoplasma are the smallest of all cellular organisms. They produce superoxide yet have no SOD to destroy it. The liposaccharides associated with mycoplasma, known as lipoglycans, are similar to the lipopolysaccharides of endotoxin.

If a patient has recurring low levels of endotoxin in the circulation and has low levels of antioxidants for protection, a mycoplasma infection might be all that would be required to induce injury and eventual demyelination.

Conclusion

It is true that one causative factor in MS is the chance similarity between the amino acid sequence of certain viruses and the sequence of certain proteins comprising myelin, and the possibility for infection by such viruses is inevitable, it would appear that an attempt to avoid this factor would be futile. In addition, if it is true that a genetic predisposition to MS is instrumental, an attempt to modify or alter this factor is also futile.

And yet, it appears that in certain societies and in certain geographical locations MS is either unknown or extremely rare. From these realizations it is indicated that other subtle and as yet unknown factors including certain aspects of diet and lifestyle may be involved in the etiology of MS.

The established relationship between MS and oxidative stress has genetic, dietary and lifestyle implications. The ability to neutralize the many members of the ROTS family of oxidants generated by normal metabolic processes occurring in all individuals, is related to many factors including age, diet (geographical location included) and familial background (genetics).

Viruses may not be the only infectious agents involved in MS etiology. Infection by those bacteria capable of generating endotoxin including those of the mouth, intestines or other locations are certain candidates as causative agents. In addition, mycoplasma are also suspect as causative agents in MS in relation to the similarity between their toxic byproducts and bacterial endotoxins. Certain mycoplasma are known to be instrumental in some cases of arthritits, pneumonia and other degenerative diseases.

Although avoiding the occurrence of MS may be virtually impossible, an efficient antioxidant capability coupled with a defensive immune system, both cellular and humoral (related to diet) to protect against infection, should greatly lower the incidence of MS.

Everything known at the present time about the nature of MS points in the direction of increased antioxidant capability coupled with greater nutrition as the most effective therapy. An increased understanding of the metabolic processes related to myelin formation and remyelination will also undoubtedly shed new light on this mysterious disease.

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